

What is claimed is:

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1. A method of providing an iron oxide complex for administration to a mammalian subject, the method comprising:  
producing a reduced polysaccharide iron oxide complex; and  
sterilizing the complex by autoclaving.

2. A method according to claim 1, wherein the reduced polysaccharide is a reduced polymer of glucose.

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3. A method according to claim 2, wherein the reduced polymer of glucose is a reduced dextran.

4. A method according to claim 1, wherein the reduced polysaccharide is produced  
15 by reacting a polysaccharide with a reagent selected from the group consisting of: a borohydride salt, and hydrogen in the presence of an hydrogenation catalyst.

5. A method of providing an iron oxide complex for administration to a mammalian subject, the method comprising:  
20 producing a derivatized reduced polysaccharide iron oxide complex; and  
sterilizing the complex by autoclaving.

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6. A method according to claim 5, wherein producing the complex includes derivatizing a reduced polysaccharide by carboxyalkylation.

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7. A method according to claim 6, wherein the carboxyalkylation is a carboxymethylation.

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~~8~~ A method according to claim ~~7~~<sup>5</sup>, wherein the reduced polysaccharide is a reduced dextran.

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~~9~~ A method according to claim ~~8~~<sup>16</sup>, wherein the administration to a mammalian  
5 subject is administration to a human.

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10 10. A method according to claim 5, wherein the derivatized, reduced polysaccharide isolated as the sodium salt does not contain an infrared absorption peak in the region of about 1650 cm<sup>-1</sup> to about 1800 cm<sup>-1</sup>.

11. A method according to claim 5, wherein producing the derivatized reduced polysaccharide is achieved at a temperature of less than about 50°C.

12. A method according to claim 11, wherein producing the derivatized reduced  
15 polysaccharide is achieved at a temperature of less than about 40°C.

13. A method according to claim 5, wherein the iron oxide is superparamagnetic.

14. A method of formulating a dextran composition for pharmacological use  
20 wherein the composition has decreased toxicity in comparison to native dextran, comprising providing a dextran; and reacting the dextran with one of a reducing agent selected from the group consisting of a borohydride salt, and hydrogen in the presence of an hydrogenation catalyst.

25 15. A method according to claim 14, wherein the pharmacological use is in vivo administration to a mammalian subject as a plasma extender.

16. An improved method of administering to a mammalian subject a polysaccharide composition of the type wherein the composition includes dextran such that

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the composition provides reduced toxicity, wherein the improvement comprises utilizing a reduced polysaccharide in formulation of the composition.

17. An improved method of administering to a mammalian subject a polysaccharide in a manner that the composition provides reduced toxicity, wherein the improvement comprises utilizing a reduced polysaccharide in formulation of the composition.

18. A reduced polysaccharide iron oxide complex, such complex being stable at a temperature of at least about 100°C.

19. A reduced polysaccharide iron oxide complex according to claim 18, such complex being stable at a temperature of about 121°C.

20. A reduced polysaccharide iron oxide complex according to claim 19, such complex being stable at a temperature of at least about 121°C for a period of time effective to sterilize the complex.

21. A reduced polysaccharide iron oxide complex according to claim 18, wherein the reduced polysaccharide is derivatized.

22. A reduced polysaccharide iron oxide complex according to claim 21, wherein the derivatized reduced polysaccharide is a carboxyalkyl reduced polysaccharide.

23. A reduced polysaccharide iron oxide complex according to claim 22, wherein the carboxyalkyl is selected from the group consisting of carboxymethyl, carboxyethyl and carboxypropyl.

24. A reduced polysaccharide iron oxide complex according to claim 23, wherein the reduced polysaccharide is a reduced dextran.

5 25. A reduced polysaccharide iron complex according to claim 22, wherein the derivatized reduced dextran is a carboxymethyl reduced dextran.

10 26. A reduced polysaccharide iron oxide complex according to claim 24, wherein the amount of derivatization of the reduced dextran is at least about 750 micromole of carboxyl groups per gram of polysaccharide, wherein said composition has reduced toxicity in a mammal relative to a composition with a lower amount of derivatization.

15 27. A reduced polysaccharide iron oxide complex according to claim 26, wherein the level of derivatization of the reduced dextran is at least about 900 micromole of carboxyl groups per gram of polysaccharide, wherein said composition has reduced toxicity in a mammal relative to a composition with a lower amount of derivatization.

20 28. A reduced polysaccharide iron oxide complex according to claim 27, wherein the amount of derivatization of the reduced dextran is at least about 1,100 micromole of carboxyl groups per gram of polysaccharide, wherein said composition has reduced toxicity relative to composition with a lower amount of derivatization.

25 29. A reduced polysaccharide iron oxide complex according to claim 24, wherein the amount of derivatization of the reduced dextran is less than about 1300 micromole of carboxyl groups per gram of polysaccharide, wherein said complex remains a colloidal suspension without substantial aggregation.

30. A method of formulating a dextran composition for pharmacological use and having decreased toxicity to a subject in comparison to native dextran, the method comprising:

providing dextran; and  
reacting the provided dextran with a borohydride salt or hydrogen in the presence of a hydrogenation catalyst followed by carboxymethylation, the carboxymethylated reduced dextran composition having decreased toxicity.

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31. A method according to claim 30, having the further step after the reacting step of sterilizing the carboxymethylated reduced dextran composition.

10 32. A method according to claim 31, having the further step after the sterilizing step of providing the sterile composition as a single dosage unit.

33. A method according to claim 31, having the additional step of administering the composition to a mammal in need of a plasma extender.

15 34. A product for use as a plasma extender produced by the method of claim 31.

20 35. An improved method of administering to a mammalian subject a polysaccharide in a manner that the composition provides reduced toxicity, wherein the improvement comprises utilizing a derivatized reduced polysaccharide in formulation of the composition.

25 36. An improved method of administering to a mammalian subject a polysaccharide composition of the type wherein the composition includes dextran in a manner that the composition provides reduced toxicity, wherein the improvement comprises utilizing carboxymethylated reduced dextran in lieu of dextran in the formulation.

37. A method of formulating for pharmacological use a dextran composition having increased pH stability in comparison to native dextran, the method comprising:  
providing a dextran; and

reacting the dextran with a borohydride salt or hydrogen in the presence of an hydrogenation catalyst, the reduced dextran providing a formulation having a stable pH.

38. A method of formulating for pharmacological use a dextran composition  
5 having increased pH stability in comparison to native dextran, the method comprising:  
providing a dextran;  
reducing the dextran with a borohydride salt or hydrogen in the presence of  
an hydrogenation catalyst; and  
carboxymethylating the reduced dextran, such that the carboxymethylated  
10 reduced dextran produces a formulation having a stable pH.

39. A method according to claim 38, further comprising after the  
carboxylating step, sterilizing the carboxymethylated reduced dextran formulation by  
autoclaving.

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40. A method according to claim 39, further comprising administering the  
sterilized carboxymethylated reduced dextran formulation to a subject in need of a plasma  
extender.

20 41. A method according to claim 38, further comprising after the  
carboxymethylation step, providing a solution of an iron salt to form a carboxymethylated  
reduced dextran iron colloid formulation having decreased toxicity.

25 42. A method according to claim 41, further comprising after the step of  
providing a solution of an iron salt, sterilizing the carboxymethylated reduced dextran iron  
formulation by autoclaving.

43. A method according to claim 38, wherein the pharmacological use comprises  
administering the formulation to a subject in need of iron.

44. A method according to claim 43, wherein the subject in need of iron is selected from the group of: a cancer patient, a gastroenteritis patient, and an erythropoietin recipient.

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45. A method according to claim 41, wherein the pharmacological use comprises administering to a subject an effective dose of the formulation to obtain enhanced magnetic resonance imaging (MRI) of a tissue or organ.

46. A method according to claim 45, wherein administering an effective dose of the carboxymethylated reduced dextran iron formulation to obtain an MRI is followed by administering a further effective dose, to obtain a further MRI.

15 47. A method according to either of claims 46, wherein the effective dose is about 0.1 to about 4.0 mg of iron per kg body weight of the subject.

48. A method according to claim 47, wherein the effective dose is about 0.2 to about 0.6 mg of iron per kg of body weight of the subject.

20 49. A method according to claim 47, wherein an effective dose is about 0.4 to about 1.0 mg of iron per kg of body weight of the subject.

50. A method according to claim 47, wherein the effective dose is about 1.0 to about 4.0 mg of iron per kg of body weight of the subject.

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51. A method according to claim 46, wherein an interval of time between administering the effective dose and administering the further effective dose is less than one hour.

52. A method according to claim 51, wherein the interval of time is less than thirty minutes.

53. A method of providing a contrast agent for in vivo MRI of a subject, comprising the steps of:  
formulating a composition which is a carboxymethylated reduced coated ultrasmall superparamagnetic iron oxide colloid; and  
terminally sterilizing the composition by autoclaving.

54. A method of providing a hematinic agent for treating a subject deficient in iron, comprising the steps of:  
formulating a composition which is a carboxymethylated reduced coated ultrasmall iron oxide colloid; and  
~~terminally sterilizing the composition by autoclaving.~~

55. A method according to claim 53 or 54, having the further step of providing the autoclaved composition in a unit dosage.

56. A kit containing multiple dosages of the agent prepared by the method of claim 55.